Specification

The disclosure is objected to because, according to the Examiner, "the cross reference to the related applications set forth on page 1 incorrectly claims priority to application 09/133,119 as a divisional application, which is incorrect as no restriction requirement was set forth in the '119 application."

Applicants respectfully traverse this objection. Neither 37 C.F.R. §1.53(b) nor 35 U.S.C. §120 or §121 require that the parent of a divisional application must have been subject to a restriction requirement. In fact, as stated in the MPEP §201.06 at page 200-20, col. 1, lines 6-10:

> A later application for an independent or distinct invention, carved out of a pending application and disclosing and claiming only subject matter disclosed in the earlier or parent application, is known as a divisional application or "division."

MPEP §201.11 at page 200-66, col. 2, lines 10-20 goes on to state:

> The term "continuity" is used to express the relationship of copendency of the same subject matter in two different applications of the same inventor. The second application may be referred to as a continuing application when the first application is not a provisional application. Continuing applications include those applications which are called divisions, continuations, and continuations-in-part. As far as the right under the statute is concerned the name used is immaterial, the names being merely expressions developed for convenience.

Thus, Applicants are entitled to the benefit of their priority claim, regardless of the label used to identify the continuing application. Reconsideration and withdrawal of the rejection are respectfully requested.

Additionally, the Examiner has also objected to the specification as not complying with 1.821(d) of the Sequence Rules and Regulations. Specifically, the Examiner states that Figures 27 and 28 set forth amino acid and polynucleotide sequences without assigned identifiers.

Although the Examiner stated that Figure 28 sets forth amino acid and polynucleotide sequences without assigned identifiers, this appears to be a typographical error. Figure 28 is a schematic illustration of the construction of the vectors used to express the heavy chain of the

immunoreceptors and contains no amino acid and polynucleotide sequences. It appears that the Examiner meant to refer to Figures 27 and 29.

Applicants wish to thank the Examiner for her January 14, 2003, telephone conference with the undersigned, providing additional comments and suggestions regarding this matter.

Figure 27 is a schematic illustration of the construction of a cM-T412 heavy chain so that it has a unique cloning site for insertion of foreign genes such as p55 and p75. Figure 29 is a schematic illustration of the construction of a cM-T412 light chain so that it has a unique cloning site for insertion of foreign genes such as p55 and p75. In compliance with 37 C.F.R. §1.821(d), the Brief Description of the Drawings for Figure 27 and Figure 29 has been amended to include the relevant sequence identifiers, as requested by the Examiner. Reconsideration and withdrawal of the rejection are respectfully requested.

Oath/Declaration

The Examiner states that the oath or declaration is defective because it claims priority as a divisional application to 09/133,119 (the '119 application).

Applicants respectfully traverse this rejection. The Declaration does not claim priority to the '119 application. The Declaration is a copy of the Declaration filed in the '119 application and was subsequently carried forward into the present application in compliance with 37 C.F.R. §1.63(d). Moreover, Applicants are entitled to their priority claim, as set forth above. Therefore, the Declaration is not defective. Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

Replacement copies of the co-pending applications submitted with the Information Disclosure Statement (IDS) filed on April 2, 2002, are submitted herewith, along with a copy of the IDS, 1449 form and date-stamped postcard receipt. Entry of the IDS is respectfully requested. The Examiner is requested to return a copy of the list of pending applications (noted on page 3 in the Transmittal of IDS) indicating which references were considered with the next office communication. Applicants believe no additional fee is required because the IDS was

previously filed. It is requested that the information disclosed in the IDS be made of record in this application.

Rejection of Claims 1-15 and 17-32 Under 35 U.S.C. §112, Second Paragraph

Claims 1-15 and 17-32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants will address the Examiner's objections to the particular claims in the order that they were presented by the Examiner.

Claims 15 and 32, which recite "wherein the antibody is produce recombinantly", were rejected because, according to the Examiner, it is unclear how the method of producing the antibody influences the material properties of the claimed antibodies.

Product by process claims are proper under 35 U.S.C. §112, second paragraph, so long as it is clear that the claim is directed to the product and not the process. (MPEP §2173.05(p)). Applicants' claimed chimeric antibody comprises at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region. Claims 15 and 32 recite one method for producing the chimeric antibody. Thus, Claims 15 and 32 are definite and distinctly claim that which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 5 and 22, which recite "physiological conditions", were rejected because, according to the Examiner, it is unclear if the physiological conditions encompass physical conditions of osmolality and pH, such as those found in physiological saline, or if physiological conditions encompass *in vivo* conditions, such as those found in the peripheral blood of an animal. For purposes of examination, the Examiner read the phrase "physiological conditions" as those found *in vivo*.

Applicants respectfully traverse this rejection. The phrase "physiological conditions" is a standard phrase used in the art to define the conditions which replicate, are compatible with, or are identical to, those found *in vivo*. For example, if an antibody is to be used to treat a disorder in a subject, it is important to determine the antibody's ability to bind its ligand under the

conditions that would be found within the subject. Even if the binding studies are to be performed *in vitro*, one of skill in the art would use conditions which would replicate, or be compatible with, the *in vivo* physiological conditions, so that the antibody would be useful for clinical therapies. One of skill in the art would clearly understand the term "physiological conditions" as used in Applicants' claims. Thus, Claims 5 and 22 are definite and distinctly claim that which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 7 and 24, which recite " high affinity", were rejected because, according to the Examiner, the term "high affinity" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree. For purposes of examination, the Examiner defined "high affinity" as the ability to block the activity of TNF-α, *in vitro*.

Applicants respectfully traverse this rejection. The term " high affinity" is a standard term used by one of skill in the art to describe an antibody's affinity for its ligand regardless of its ability to block the activity of TNF-α, *in vitro*. An antibody can bind to its ligand with high affinity and, yet, have no effect on the activity of the ligand. The **general** use of the term "high affinity" is evidenced by Möller *et al.* (*Cytokine*, v.2(3): 162-169 (1990), cited by the Examiner in the below 35 U.S.C. §103(a) rejection) at page 165, col. 2, lines 22-25, where Möller *et al.* use the phrase "high affinity monoclonal antibodies". The only support relied upon in Möller *et al* for this phrase is the affinity constants for the antibodies as shown in Table 1 of Möller *et al.* One of skill in the art would understand, based on an antibody's binding affinity for its ligand, whether the antibody bound to its ligand with low, moderate or high affinity. Thus, Claims 7 and 24 are definite and distinctly claim that which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 17 was rejected as vague and indefinite in the use of "cA2" as the sole means of identifying the claimed antibody. According to the Examiner:

> The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct antibodies. Amendment of the claims to

include the depository accession number or sequence identifiers is required, because deposit accession numbers and sequence identifiers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

Applicants respectfully traverse this rejection. Applicants have enclosed scientific articles and press releases referring to Applicants' claimed monoclonal antibody as "cA2". (See Exhibits A-B). These articles are representative of the general knowledge of one skilled in the art and demonstrate that the identifier "cA2" is not indefinite. Rather, cA2 is recognized by those of skill in the art as a unique indentifier of Applicants' chimeric monoclonal antibody. Moreover, the Examiner has already allowed claims to issue which refer to the instant monoclonal antibody as cA2. (See, e.g., the claims of U.S. Patent No. 6,284,471, attached hereto as "Exhibit C" for the Examiner's convenience). Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1 and 18, which recite "epitope specific for human TNF alpha", were rejected as vague and indefinite because, according to the Examiner, it is unclear if the specificity is to be evaluated in relation to TNF alpha of other species such as rabbit or mouse, or if the specificity is to be evaluated in relation to human TNF-beta or gamma.

Applicants respectfully traverse this rejection. A claim and its limitations are interpreted in light of the teachings of the Specification. Applicants clearly teach that the claimed antibodies are specific for human TNF-α when evaluated in relation to TNF-α of other species (*i.e.*, rabbit or mouse) **and** when evaluated in relation to human TNF-beta or gamma. (See, for example, the instant specification at Example X at page 81, line 13 to page 82, line 10). Thus, Claims 1 and 18 are definite and distinctly claim that which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 11-13, 28-30 and 52-54 Under 35 U.S.C. §112, first paragraph

Claims 11-13, 28-30 and 52-54 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states that:

> The specification sets forth on page 72 and figure 3 the results of an in vitro cytotoxicity assay with the cA2 antibody. It is noted that in figure 3 the concentration of the antibody is given in ng/ml. Claims 11-13, 28-30 and 52-54 are drawn to ID50s on the order of ug/ml and ng/ml. Given the inconsistencies within the specification, one of skill in the art would not know how to make or use the claimed antibodies having the recited ID50 values, because one of skill in the art would not be able to ascertain the actual ID50 of the cA2 antibody. Therefore, one of skill in the art would be subject to undue experimentation in order to make and use the claimed antibodies having specific ID50 values.

Applicants respectfully traverse this rejection. In Figure 3, the concentration of the antibody is given in ng/ml. However, Applicants draw the Examiner's attention to the 1000 ng/ml concentration point shown in Figure 3. 1000 ng/ml is the same as 1 μg/ml because 1 ng equals 10^{-3} μg. Therefore, there are no inconsistencies within the specification. One of skill in the art would know how to make and use the claimed antibodies having the recited ID50 values, because one of skill in the art would be able to convert ng/ml to μg/ml, and vice-versa, without undue experimentation and, thus, ascertain the actual ID50 of the cA2 antibody. Moreover, Applicants teach methods which can be used to determine TNF neutralizing activity of a TNF neutralizing compound, and teach the ID50 values obtained for the claimed antibodies. (See the Detailed Description at page 53, lines 23-27, and Examples II and XI). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-10, 14, 15, 18-27, 31, 32 and 34-51 Under 35 U.S.C. §112, first paragraph

Claims 1-10, 14, 15, 18-27, 31, 32 and 34-51 are rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner:

> the specification, while being enabling for chimeric antibodies containing all of the variable regions of the parent non-human antibody, said chimeric antibody having unspecified binding affinity for TNF alpha; the entire cA2 antibody; and antibodies comprising the entire light chain of cA2 (SEQ ID NO: 3) and the entire heavy chain of cA2 (SEQ ID NO: 5), does not reasonably provide enablement for antibodies or polypeptides which have only

> a single light or heavy of cA2, antibodies which compete with cA2 for binding to hTNF, chimeric antibodies which are not cA2 having Ka values of at least 1 x 10^8 L/mole or 1 x 10^9 L/mole, or fragments of antibodies or polypeptides, thereof.

For convenience, the remainder of this rejection will be addressed under the appropriate subheadings as outlined by the Examiner.

(A) Rejection of Claims 8-10 and 25-27 as drawn to chimeric antibodies other than cA2 which compete for binding with cA2 and have affinity constants of 1 x 10^8 or 1 x 10^9.

According to the Examiner, given the teachings of the specification regarding the unexpected high binding affinity of the cA2 antibody, the teachings of Mateo (Mateo *et al.*, *Hybridoma*, v.19, pp. 463-471 (2000)) regarding the expectation of lower binding affinity for a chimeric antibody, and the teachings of Adair (Adair *et al.*, WO 92/11383) regarding the necessity of altering framework regions to improve binding affinity, it can be concluded that the specification is lacking in teachings on how to make other chimeric antibodies which bind to TNF-α with the claimed affinity constants or having the ability to competitively inhibit the binding of cA2 to TNF-α. Thus, according to the Examiner, given the lack of teachings and the unpredictability of the art as exemplified by Mateo and Adair, a person of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make chimeric antibodies other than cA2 which would have these claimed elements.

Applicants respectfully disagree. Applicants direct the Examiner's attention to the Federal Circuit decision in *In re Wands,* 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)(a copy of which is attached hereto as Exhibit D for the Examiner's convenience). The claims at issue in *Wands* recited methods for immunoassay of HbsAg using high affinity monoclonal antibodies that the Appellants found to have unexpectedly high sensitivity and specificity. The position of the PTO was that the data presented by Appellants showed that the production of high-affinity IgM anti-HBsAG antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

As stated by the court in *In re Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening." The court recognized that the nature of

monoclonal antibody technology is such that it involves screening hybridomas to determine which ones secrete antibodies with desired characteristics, and that practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. The court went on to state that "in the monoclonal art it appears that experimentation is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen."

Applicants contend that the written Specification fully enables the practice of the claimed invention because the claimed antibodies can be made from readily available starting materials using methods that are well known in the art. For example, it teaches a method of producing the claimed chimeric antibodies according to the present invention (See instant Detailed Description at page 32, lines 7 through 24 and Examples III-IX). Additionally, it teaches methods of cloning a polynucleotide encoding an anti-TNF variable or constant region. (See, for example, instant Detailed Description at page 28, line 8 through page 30, line 4 and page 30, line 5 through page 31, line 2). Furthermore, the instant specification teaches that preferred anti-TNF mAbs also include those which will competitively inhibit *in vivo* the binding to human TNF-α of anti-TNF-α murine mAb A2, chimeric mAb cA2, or an antibody having substantially the same specific binding characteristics, as well as fragments and regions thereof. (See instant Detailed Description at page 19, line 25 through page 20, line 2). It also teaches preferred methods for determining mAb specificity and affinity (See, for example, instant Specification at Examples X and XI). Thus, a person of skill in the art would not be subject to undue experimentation without reasonable expectation of success in order to make chimeric antibodies other than cA2 which would have these claimed elements.

Furthermore, MPEP §2164.08 states that all questions of enablement are evaluated against the claimed subject matter. All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Thus, the determination of the propriety of a rejection based upon the scope of a claim relative to the scope of the enablement involves two stages of inquiry. The first is to determine how broad the claim is with respect to the disclosure. The second is to determine if one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 169 USPQ 236, 239 (CCPA 1971). Therefore, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, *e.g.*, *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

In the instant application, Claims 9, 10, 26 and 27 recite chimeric antibodies comprising part of a human immunoglobulin constant domain and part of a non-human variable region, said antibodies binding to TNF-α with affinity constants of at least 1×10^8 or 1×10^9. Additionally, Claims 8 and 25 recite chimeric antibodies which competitively inhibit the binding of cA2 to TNF-α. These claims define the scope of protection sought by Applicants. Thus, the scope of enablement disclosed in the instant application must only bear a "reasonable correlation" to these claimed chimeric antibodies. As long as the Specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

As discussed above, the instant Specification provides ample teachings such that one of skill in the art would not be subject to undue experimentation in order to make or use the claimed antibodies. Thus, the skilled artisan is enabled to use the claimed invention commensurate in scope with the claims, thereby, meeting the requirements established by *In re Fisher*. Reconsideration and withdrawal of the invention are respectfully requested.

(B) Rejection of Claims 1-10, 14, 15, 18-27, 31, 32, 34-39 and 40-51 and 55 as drawn to chimeric antibodies comprising part of SEQ ID NO: 3 and part of SEQ ID NO: 5, polypeptides comprising either SEQ ID NO: 3 or SEQ ID NO: 5, polypeptides comprising fragments of either SEQ ID NO: 3 or SEQ ID NO: 5 and fusion proteins comprising either SEQ ID NO: 3 or SEQ ID NO: 5 and fragments of said fusion proteins.

The Examiner has rejected Claims 1-10, 14, 15, 18-27, 31, 32, 34-39 and 40-51 and 55. Claims 3, 20, 34-36, 38, 39, 43, 44, 46 and 47 have been cancelled herein. According to the Examiner, it is "well established" in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a

given antibody; therefore, the Examiner relies on Paul (Paul, *Fundamental Immunology*, 3rd Ed., page 292-293 (1993)) to state that it cannot be expected that antibodies or polypeptide comprising less than the full variable regions of SEQ ID NO: 3 or SEQ ID NO: 5 will form the identical ligand binding surface. Thus, according to the Examiner, it is unlikely that antibodies, polypeptides or fusion proteins as defined by the claims which contain less than the full heavy or light chain variable regions of the cA2 antibody and fused to any human framework sequence or comprised of any polypeptide sequence would have the required binding function. Therefore, the Examiner states that the specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims and undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Applicants respectfully disagree. Paul describes the general structure of an antibody and states that the vast sequence possibilities in the variable domain, and the unique folding of variable region polypeptides, result in the diverse repertoire of antibody binding specificities. The teachings of Paul do not support the statements made by the Examiner regarding Paul's applicability to the instant claims. Applicants are not claiming that antibodies or polypeptides comprising less than the full variable regions of SEQ ID NO: 3 or SEQ ID NO: 5 will form an identical ligand binding surface as antibodies or polypeptides comprising SEQ ID NO: 3 or SEQ ID NO: 5. Rather, Applicants are claiming chimeric antibodies, polypeptides, or a fusion protein, comprising all or part of the light and heavy chain variable regions of a parent non-human antibody and polypeptide fragments of SEQ ID NO: 3 and/or SEQ ID NO: 5 which competitively inhibit the binding of cA2 to TNF-α. Moreover, Applicants have provided ample support to cover the scope of the instant claims.

The only relevant concern regarding the scope of enablement provided to one skilled in the art by the disclosure is whether the scope of enablement is commensurate with the scope of protection sought by the claims. *In re Moore*, 169 USPQ 236, 239 (CCPA 1971). Thus, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

In the instant application, the scope of enablement disclosed in the instant application must only bear a "reasonable correlation" to chimeric antibodies comprising part of SEQ ID NO:

3 and part of SEQ ID NO: 5, polypeptides comprising either SEQ ID NO: 3 or SEQ ID NO: 5, polypeptides comprising fragments of either SEQ ID NO: 3 or SEQ ID NO: 5, fusion proteins comprising SEQ ID NO: 3 or SEQ ID NO: 5 and fragments of said fusion proteins. As long as the Specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1978).

As stated above, Applicants provide ample guidance within the specification (which is over 160 pages long) and figures to enable the rejected claims. Claims 1-10, 14, 15, 18-27, 31, 32 and 34-39 encompass chimeric antibodies comprising all or part of the light and heavy chain variable regions of a parent non-human antibody. Claims 40-45 and 48-51 encompass polypeptides and a fusion protein comprising all or at least one binding fragment of the light chain or heavy chain variable regions, or polypeptide fragments of SEQ ID NO: 3 and/or SEQ ID NO: 5 which competitively inhibit the binding of cA2 to TNF-α. Although the Examiner stated that all of Claims 45-59 fit this category, this appears to be a typographical error. Claims 52-54, which are similar in format to Claims 11-13 and 28-30, which were not rejected, appear to be outside this category of claims, and there are no pending Claims 56-59.

The Specification teaches a method of producing a chimeric antibody according to the present invention (See the Detailed Description at page 32, lines 7 through 24). The Specification also teaches that preferred anti-TNF mAbs, as well as fragments and regions thereof, are those which will competitively inhibit *in vivo* the binding to human TNF-α of anti-TNF-α murine mAb A2, chimeric mAb cA2, or an antibody having substantially the same specific binding characteristics. (See the Detailed Description at page 19, line 25 through page 20, line 2). Applicants' Specification also teaches preferred methods for determining mAb specificity and affinity by competitive inhibition (See, for example, Specification at Examples X and XI). Contrary to the Examiner's assertion, the Specification teaches methods of cloning a polynucleotide capable of expressing a protein which competitively inhibits the binding of an anti-TNF antibody, such as A2 or cA2, and which has a nucleotide sequence that is capable of encoding polypeptides that have the same amino acid sequence as anti-TNF antibodies or fragments thereof. (See, for example, instant Detailed Description at page 28, line 8 through page 31, line 2).

Applicants' Specification teaches one skilled in the art how the claimed antibodies were prepared and how the claimed antibodies were tested for their functional properties. Therefore, the disclosure bears a reasonable correlation to the entire scope of the claims and enables one of skill in the art to make and use the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 Under 35 U.S.C. §103(a)

Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 are rejected under 35 U.S.C. §103(a) as being unpatentable over Möller *et al.* (*Cytokine*, v.2, pp.162-169 (1990))("Möller") in view of Zerler (EP 380,068) as evidenced by Morrison *et al.* (In: Antibody Engineering, Ed. Borrebaeck, p. 291 (1995))("Morrison"). The Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a chimeric antibody having a IgG1 constant region, wherein the variable region was derived from murine mAb195 antibody of Möller.

Applicants respectfully traverse this rejection. Applicants' invention is drawn to chimeric antibodies which bind an epitope specific for human TNFα. In contrast, the antibodies of Möller *et al.* are not chimeric, rather they are mouse monoclonal antibodies. One of the main problems associated with the use of murine antibodies in pharmaceutical treatments in humans was the possibility that a harmful immunological Human Anti-Mouse Antibody (HAMA) response, can occur once the murine is administered to a human. Applicants were the first to successfully incorporate human sequence into a neutralizing murine antibody for TNFα, to reduce the immunological effect while still maintaining the high binding affinity and pharmaceutical effectiveness of the parent antibody. Möller *et al.* fail to report a HAMA response or suggest the manufacture or use of a chimerized antibody to prevent the response in clinical treatment, or that chimerizing the disclosed antibody would sufficiently reduce the HAMA response to be therapeutically advantageous. Thus, one of skill in the art would not be motivated, and would be without a reasonable expectation of success, to modify the teachings of Möller *et al.* to obtain the claimed chimeric antibodies.

Furthermore, Möller *et al.* do not describe antibodies which possess the characteristics of Applicants' claimed chimeric antibodies. For example, Möller *et al.* teaches that monoclonal

antibody mAb 114 shows cross-reactivity with TNF-α of cynomolgus, rhesus and baboon; mAb 199 does not neutralize the cytotoxicity of human TNF-α. In fact, the Möller *et al.* reference does not describe the *in vivo* neutralizing ability of any antibody described for use in the treatment of humans. The *in vitro* studies taught in Möller *et al.* were limited to determining the ability of their anti-TNF antibodies to bind to TNF and to alter some features of its biological activity. However, these *in vitro* studies do not suggest the clinical protocols or results of effective administration of anti-TNF antibodies in humans. They do not establish that anti-TNF antibody administration would have any effect on TNF-mediated disease *in vivo*, or the magnitude and duration of the clinical response and possible adverse reactions of that therapy. TNFα is known to contain many epitopes. A skilled artisan, on the basis of the information disclosed in these references, would not conclude that any of the prior art antibodies are identical to or contain the features of the antibodies claimed by Applicants.

To maintain a rejection based on obviousness, it must be demonstrated that at the time of the invention, one of skill in the art would have been motivated to chimerize the murine antibodies taught by Möller *et al.* to produce Applicants' claimed compounds with a reasonable expectation of success. See *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1442 (Fed. Cir. 1991). Zerler *et al.* fails to provide this necessary motivation.

As discussed above, the Möller *et al.* reference does not provide the teachings for producing TNF neutralizing antibodies that can be used for *in vivo* diagnostic or therapeutic uses in humans. By contrast, Applicants' claimed antibodies have been demonstrated to be capable of neutralizing TNFα in a clinical setting with superior results. Furthermore, Zerler *et al.* does not provide that which Möller *et al.* reference lacks. Zerler *et al.* does not teach TNF neutralizing antibodies. Rather, it is the object of Zerler *et al.* to provide a generic expression system for producing chimeric antibodies that allows for insertion of a non-human variable region without mutagenesis of the variable region.

As noted by the Examiner, Zerler *et al.* does not teach that the recombinant chimeric antibody from the disclosed method would contain two light chains and two heavy chains. The Examiner relies on the teaching by Morrison *et al.* (at page 291), to provide this support. According to the Examiner, Morrison *et al.* teaches that transfectomas generally secrete IgGs as H2L2 (two heavy chains and two light chains). However, this is irrelevant since one of skill in

the art would not have been motivated to chimerize the murine antibody taught by Möller *et al.* to produce Applicants' claimed compounds with a reasonable expectations of success based upon the teachings of Zerler *et al.*

Thus, the combination of references do not teach or suggest the preparation of chimeric antibodies which bind TNFα, do not provide a reasonable expectation of achieving a chimeric antibody of reduced immunogenicity and/or possessing a therapeutic benefit *in vivo* and do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. As such, the claimed invention is not obvious over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-7, 15, 18-24 and 32 Under 35 U.S.C. §103(a)

Claims 1-7, 15, 18-24 and 32 are rejected under 35 U.S.C. §103(a) as being unpatentable over Möller *et al.* (*Cytokine*, v.2, pp.162-169 (1990))("Möller") in view of Zerler (EP 380,068) as evidenced by Morrison *et al.* (In: Antibody Engineering, Ed. Borrebaeck, p. 291 (1995))("Morrison") as applied to Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 above, and further in view of Socher et al. (*PNAS* v.84, pp. 8829-8833 (1987))("Socher") as evidenced by the abstract of Goh (*Annals of the Academy of Medicine*, v.19, pp. 235-239 (1990)).

Applicants respectfully disagree. Claims 3 and 20 have been cancelled herein, thus rendering the rejection moot as it applies to these claims. Additionally, for reasons discussed above, Claims 1, 2, 4-7, 15, 18, 19, 21-24 and 32 are not obvious over Möller in view of Zerler as evidenced by Morrison.

Socher does not provide that which Möller, Zerler and Morrison lack. According to the Examiner, Socher teaches polyclonal antibodies raised against fragments of human tumor necrosis factor (hTNF). The only Goh *et al.* teaching relied upon by the Examiner is that TNF-α is synonymous with cachectin. Applicants do not contest that TNF-α is synonymous with cachectin. However, Socher does not teach or suggest the chimeric monoclonal antibody claimed by Applicants.

First, Socher teaches polyclonal antisera that were raised against several fragments of hTNF and tested for their ability to block hTNF binding to its receptor. A polyclonal serum, even if "purified" from an immune antiserum (*i.e.*, all antibody molecules specific for the same

substance and sharing the same overall immunoglobulin structure) will be a heterogeneous mixture of molecules of different subclasses, different affinities and different specificities. In contrast, a monoclonal antibody contains a substantially homogeneous population of antibodies specific to antigens, which population contains substantially similar epitope binding sites. (See, for example, instant Specification at page 17, lines 9-13).

Second, of all the various polyclonal antisera raised by Socher, *only* antisera raised against hTNF amino acids 1-15 or hTNF amino acids 1-31 and antisera against whole hTNF blocked binding. (See Abstract at lines 18-20, and the title of Socher *et. al.*). Socher found that in both cytolysis and LPL suppression assays, IgGs obtained from antisera directed against hTNF (65-79), hTNF (98-111), and hTNF (124-141) ***failed*** to inhibit the effects of hTNF. (See page 8831, col. 2, lines 35-38). Socher concludes that antibodies (*i.e.*, polyclonal antisera) that recognize the N-terminus of hTNF block the attachment of hTNF to its cellular receptor and inhibit the biological effect of hTNF. (See Abstract at lines 22-24).

Socher provides no suggestion or motivation to one of skill in the art at the time the invention was made that Applicants' claimed antibodies would exhibit the ability to inhibit TNF-α activity. Thus, one of skill in the art would not have been motivated to combine the cited references to produce Applicants' claimed compounds with a reasonable expectation of success.

The combination of references do not teach or suggest the preparation of chimeric antibodies which bind TNFα, do not provide a reasonable expectation of achieving a chimeric antibody of reduced immunogenicity and/or possessing a therapeutic benefit *in vivo* and do not reasonably suggest that the unexpected and superior results achieved and described herein were possible. As such, the claimed invention is not obvious over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

For convenience, the four (4) double patenting rejections will be addressed in the order established by the Examiner.

Claims 34-36, 38, 39, 46 and 47 are rejected under 35 U.S.C. §101 as claiming the same invention as that of Claims 1, 3 and 5-9 of prior U.S. Patent No. 6,284,471.

Claims 34-36, 38, 39, 46 and 47 have been cancelled herein, thus rendering the rejection moot. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 4, 15, 18, 21 and 32 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3 and 5-7 of U.S. Patent No. 6,284,471.

A Terminal Disclaimer is enclosed herewith, in which the owners of 100 percent interest in the instant application, Centocor, Inc. and New York University Medical Center, disclaim the terminal part of the statutory term of any patent granted on Claims 1, 4, 15, 18, 21 and 32 in the instant application beyond the expiration date of prior Patent No. 6,284,471.

Claims 1, 4, 6, 8, 15, 18, 21, 23, 25, 32, 34-40, 48, 49 and 55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-24 and 38 of co-pending U.S. Application Serial No. 09/756,161. Claims 34-36, 38, 39 and 44 have been cancelled herein, thus rendering the rejection as it applies to these claims moot.

U.S. Application Serial No. 09/756,161 went abandoned on September 25, 2002, for failure to respond to the Office Action mailed from the United States Patent and Trademark Office on March 25, 2002.Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 17, 37, 40-45 and 50-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3 and 5-9 of U.S. Patent No. 6,284,471.

Claims 43 and 44 have been cancelled herein, thus rendering the rejection as it applies to these claims moot. Reconsideration and withdrawal of the rejection as it applies to Claim 40 are respectfully requested.

Additionally, in the Terminal Disclaimer enclosed herewith, as discussed above, the owners of the instant application, Centocor, Inc. and New York University Medical Center, also

disclaim the terminal part of the statutory term of any patent granted on Claims 17, 37, 40-42, 45 and 50-55 in the instant application beyond the expiration date of prior Patent No. 6,284,471.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

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Dated: January 21, 2003

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 15, lines 3 through 5 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figure 27 is a schematic illustration of the construction of a cM-T412 heavy chain so that it has a unique cloning site for insertion of foreign genes such as p55 and p75. (SEQ ID NOS: 20, 21, 22, 23 and 24).

Replace the paragraph at page 15, lines 8 through 9 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figure 29 is a schematic illustration of the construction of a cM-T412 light chain so that it has a unique cloning site for insertion of foreign genes such as p55 and p75. (SEQ ID NOS: 25, 26, 27, 28, 29 and 30).

Inhibition of immunoreactive tumor necrosis factor-alpha by a chimeric antibody in patients infected with human immunodeficiency virus type 1.

J Infect Dis. 1996 Jul;174(1):63-8. Unique Identifier : AIDSLINE MED/96261994

Walker RE; Spooner KM; Kelly G; McCloskey RV; Woody JN; Falloon J; Baseler M; Piscitelli SC; Davey RT Jr; Polis MA; Kovacs JA; Masur H; Lan HC; National Institute of Allergy and Infectious Diseases, Critical; Care Medicine Department, National Institutes of Health,; Bethesda, MD 20892, USA.

Abstract: Tumor necrosis factor-alpha (TNF-alpha), a proinflammatory cytokine known to stimulate human immunodeficiency virus type 1 (HIV-1) replication, has been implicated in the pathogenesis of HIV-1 infection. Inhibition of TNF-alpha by a chimeric humanized monoclonal antibody, cA2, was investigated in 6 HIV-1-infected patients with CD4 cell counts < 200/mm3. Two consecutive infusions of 10 mg/kg 14 days apart were well tolerated, and a prolonged serum half-life for cA2 (mean, 257 +/- 70 h) was demonstrated. Serum immunoreactive TNF-alpha concentrations fell from a mean prestudy value of 6.4 pg/mL (range, 4.2-7.9) to 1.1 pg/mL (range, 0.5-2.2) 24 h after the first infusion and returned to baseline within 7-14 days. A similar response was seen after the second infusion. No consistent changes in CD4 cell counts or plasma HIV RNA levels were observed over 42 days. Future studies evaluating the therapeutic utility of long-term TNF-alpha suppression using anti-TNF-alpha antibodies are feasible and warranted.

Keywords: Acquired Immunodeficiency Syndrome/BLOOD/*IMMUNOLOGY Adult Animal Antibodies/*THERAPEUTIC USE Antibodies, Monoclonal/*THERAPEUTIC USE Chimeric Proteins/PHARMACOKINETICS/*THERAPEUTIC USE Female Human *HIV-1 Male Mice Recombinant Proteins/PHARMACOKINETICS/THERAPEUTIC USE Tumor Necrosis Factor/*ANTAGONISTS & INHIB/IMMUNOLOGY JOURNAL ARTICLE
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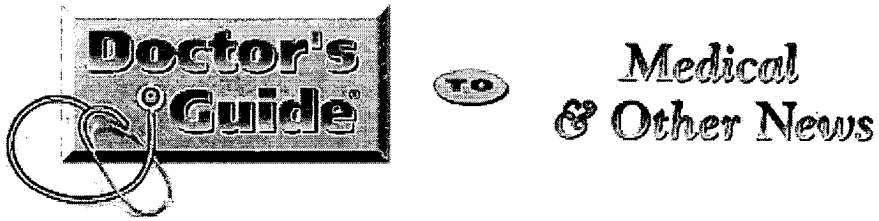

To print: Select File and then Print from your browser's menu

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Title: **New Monoclonal Antibody Effective Treatment For Crohn's Disease Therapy**
URL: http://www.pslgroup.com/dg/2802E.htm
Doctor's Guide
May 13, 1997

WASHINGTON, and MALVERN, Pa., May 13, 1997 -- Statistically significant results were released yesterday from two controlled clinical studies testing cA2(TM) (infliximab), a monoclonal antibody, in the treatment of Crohn's disease, a chronic disorder characterized by inflammation of the gastrointestinal tract. Data from both trials show that treatment with cA2 can have a beneficial effect on both the severity and number of symptoms associated with Crohn's disease.

"This kind of clinical response in Crohn's disease is unprecedented," said Stephan Targan, M.D., principal investigator and Director of the Inflammatory Bowel Disease Center at Cedars-Sinai Medical Center in Los Angeles, "and provides compelling evidence of the potential of cA2 in the treatment of Crohn's disease."

The results of these trials, which were conducted in 18 centers in North America and Europe, were announced today during Digestive Disease Week in Washington, DC. Digestive Disease Week is sponsored by the American Association for the Study of Liver Diseases, the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy and The Society for Surgery of the Alimentary Tract.

Last year, during Digestive Disease Week, Centocor released data showing a statistically significant improvement in disease activity following a single infusion of cA2. In the initial study, 65 percent of patients treated with cA2 achieved a clinical response and 33 percent of patients went into remission within four weeks of the start of treatment.

In the extension phase of this study, known as T16, which is being reported today, additional cA2 treatments were demonstrated to maintain Crohn's disease patients in clinical remission as measured by the CDAI, the Crohn's disease activity index.

In the initial phase of the T16 trial, the median CDAI of treated patients dropped from 312 to 125 eight weeks after a single cA2 infusion. Following four additional infusions, given eight weeks apart in the most recent phase of the T16 trial, cA2 maintained the CDAI reduction, with median CDAI eight weeks following the final treatment at 117 (CDAI<150 constitutes disease remission).

Data from the second trial, named T20, indicate that cA2 may be a valuable treatment for enterocutaneous fistulae, a painful, debilitating complication of Crohn's disease in which extensions occur between the bowel and the skin, mostly in the perianal area, causing drainage of mucous and/or fecal material. In this trial, approximately two-thirds of participants experienced closure of at least 50 percent of their fistulae.

In both clinical trials, onset of cA2 clinical benefit was rapid with the vast majority of responders achieving response within two weeks. In addition, cA2 was generally well tolerated in these two trials. "We have been following these studies with great interest," said Richard P. MacDermott, M. D., Immediate Past Chairperson, National Scientific Advisory Committee, Crohn's & Colitis Foundation of America (CCFA). "The results are very encouraging. It is possible that an important new therapy for Crohn's disease may be on the horizon."

In the T16 study, 73 patients who showed a clinical response eight weeks after their initial infusion of cA2 were re-randomized at week 12 to further treatment with cA2 or placebo, and infused every eight weeks for a total of four additional infusions. Those patients re-randomized to cA2 continued to experience an improvement in symptoms from baseline assessment and the percentage of patients achieving clinical remission was maintained at approximately 60 percent during the re-treatment period.

Those patients who responded to their initial infusion of cA2 and then received placebo in the re-treatment phase of the study, experienced a gradual decline in clinical effect over time. However, 19 percent of the placebo group were still in remission 48 weeks after their initial cA2 infusion.

The second study, T20, was conducted with 94 patients with draining enterocutaneous fistulae. Following a series of three cA2 infusions given two and four weeks apart, two-thirds of patients experienced closure of at least 50 percent of their fistulas (P=0.002). These patients had previously failed to respond adequately to treatment with combinations of corticosteroids, methotrexate, 6-MP/azathioprine, aminosalicylates, or antibiotics. These underlying therapies were given in conjunction with the cA2 infusions in this study. "cA2 is the first drug to ever demonstrate statistical significance in a controlled trial to close fistulas," according to Daniel Present, M.D., principal investigator and Clinical Professor of Medicine at Mount Sinai.

cA2, a monoclonal antibody, is the first of a revolutionary class of agents being studied for Crohn's disease. It is a well-tolerated, highly selective treatment that blocks activity of a key inflammatory mediator called tumor necrosis factor or TNF. cA2 is also being studied for treatment of rheumatoid arthritis.

Centocor is a biotechnology company whose mission is to develop and commercialize novel therapeutic and diagnostic products and services that solve critical needs in human health care. The company concentrates on research and development, manufacturing and market development, with a primary technology focus on monoclonal antibodies and DNA-based products.

More information about the company and cA2 can be found on Centocor's home page located at the following address. For more information about Crohn's disease or ulcerative colitis, a related disorder, contact the Crohn's & Colitis Foundation of America, at 1-800-343-3637 (website: http://www.ccfa.org).

Return to News Story Page

-continued

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

ATCGGACGTGGACGTGCAGA 20

What is claimed is:

1. A chimeric antibody comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor TNFα, wherein the non-human immunoglobulin variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

2. An immunoassay method for detecting human TNF in a sample, comprising:

(a) contacting said sample with an antibody according to claim 1, or a TNF binding fragment thereof, in detectably labeled form; and

(b) detecting the binding of the antibody to said TNF.

3. A chimeric antibody comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human tumor necrosis factor TNFα, wherein the non-human immunoglobulin variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

4. An immunoassay method for detecting human TNF in a sample, comprising:

(a) contacting said sample with an antibody according to claim 3, or a TNF binding fragment thereof, in detectably labeled form; and

(b) detecting the binding of the antibody to said TNF.

5. A chimeric antibody, comprising two light chains and two heavy chains, each of said chains comprising at least part of a human immunoglobulin constant region and at least part of a non-human immunoglobulin variable region, said variable region capable of binding an epitope of human tumor necrosis factor hTNFα, wherein said light chains comprise variable regions comprising SEQ ID NO: 3 and said heavy chains comprise variable regions comprising SEQ ID NO: 5.

6. A chimeric antibody according to claim 5, wherein the human immunoglobulin constant region is an IgG1.

7. A chimeric antibody comprising at least part of a human IgG1 constant region and at least part of a non-human immunoglobulin variable region, said antibody capable of binding an epitope specific for human TNFα, wherein the non-human immunoglobulin variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4.

8. A polypeptide comprising the amino acid sequence of SEQ ID NO: 3, wherein said polypeptide binds to hTNFα and competitively inhibits the binding of monoclonal antibody cA2 to hTNFα.

9. A polypeptide comprising the amino acid sequence of SEQ ID NO: 5, wherein said polypeptide binds to hTNFα and competitively inhibits the binding of monoclonal antibody cA2 to hTNFα.

* * * * *

of Law will be entered on the same date herewith.

ORDER AND JUDGMENT

In accordance with the Findings of Fact and Conclusions of Law entered on the same date herewith,

IT IS HEREBY ORDERED AND ADJUDGED, as follows:

1. The Nolan patent (No. 4,506,189), issued on March 19, 1985, is a valid patent.

2. By the manufacture, production, sale and distribution of its SAF-T-COTE fluorescent lamp, Trojan has infringed the Nolan patent.

3. By virtue of this infringement, Shat-R-Shield is entitled to injunctive relief. Trojan shall immediately cease and desist from the manufacture, production, sale and distribution of the SAF-T-COTE fluorescent lamp.

4. Trojan shall recall all the SAF-T-COTE fluorescent lamps sold to and still in the possession of its customers.

5. The Court having determined that Trojan's infringement was not willful and wanton, Shat-R-Shield is not entitled to treble damages.

6. Shat-R-Shield shall have no accounting for monetary damages.

7. The Court having found that this is not an exceptional case, Shat-R-Shield is not entitled to its attorney's fees.

8. All claims having been resolved as to all parties herein, this action is now DISMISSED and STRICKEN from the docket.

9. There being no just reason for delay, this is a FINAL and APPEALABLE Order and Judgment.

Court of Appeals, Federal Circuit

In re Wands

No. 87-1454

Decided September 30, 1988

PATENTS

1. Patentability/Validity — Adequacy of disclosure (§115.12)

Data disclosed in application for immunoassay method patent, which shows that applicants screened nine of 143 cell lines developed for production of antibody necessary to practice invention, stored remainder of said cell lines, and found that four out of nine cell lines screened produced antibody falling within limitation of claims, were erroneously interpreted by Board of Patent Appeals and Interferences as failing to meet disclosure requirements of 35 USC 112, since board's characterization of stored cell lines as "failures" demonstrating unreliability of applicants' methods was improper in view of fact that such unscreened cell lines prove nothing concerning probability of success of person skilled in art attempting to obtain requisite antibodies using applicants' methods.

2. Patentability/Validity — Adequacy of disclosure (§115.12)

Disclosure in application for immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring "undue experimentation," even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or "hybridomas," since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one "experiment" is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Appeal from decision of Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application for patent of Jack R. Wands, Vincent R. Zurawski, Jr., and Hubert J. P. Schoemaker, serial number 188,735. From decision of Board of Patent Appeals and Interferences affirming rejection of application, applicants appeal. Reversed; Newman, J., concurring in part and dissenting in part in separate opinion.

Jorge A. Goldstein, of Saidman, Sterne, Kessler & Goldstein (Henry N. Wixon, with them on brief), Washington, D.C., for appellant.

John H. Raubitschek, associate solicitor (Joseph F. Nakamura and Fred E. McKelvey, with him on brief), PTO, for appellee.

Before Smith, Newman, and Bissell, circuit judges.

Smith, J.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (board) affirming the rejection of all remaining claims in appellant's application for a patent, serial No. 188,735, entitled "Immunoassay Utilizing Monoclonal High Affinity IgM

Antibodies," which was filed September 19, 1980.[1] The rejection under 35 U.S.C. §112, first paragraph, is based on the grounds that appellant's written specification would not enable a person skilled in the art to make the monoclonal antibodies that are needed to practice the claimed invention without undue experimentation. We reverse.

I. *Issue*

The only issue on appeal is whether the board erred, as a matter of law, by sustaining the examiner's rejection for lack of enablement under 35 U.S.C. §112, first paragraph, of all remaining claims in appellants' patent application, serial No. 188,735.

II. *Background*

A. *The Art.*

The claimed invention involves immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype. *Antibodies* are a class of proteins (immunoglobulins) that help defend the body against invaders such as viruses and bacteria. An antibody has the potential to bind tightly to another molecule, which molecule is called an antigen. The body has the ability to make millions of different antibodies that bind to different antigens. However, it is only after exposure of an antigen that a complicated *immune response* leads to the production of antibodies against that antigen. For example, on the surface of hepatitis B virus particles there is a large protein called *hepatitis B surface antigen* (HBsAg). As its name implies, it is capable of serving as an antigen. During a hepatitis B infection (or when purified HBsAg is injected experimentally), the body begins to make antibodies that bind tightly and specifically to HBsAg. Such antibodies can be used as reagents for sensitive diagnostic tests (*e.g.*, to detect hepatitis B virus in blood and other tissues, a purpose of the claimed invention). A method for detecting or measuring antigens by using antibodies as reagents is called an *immunoassay*.

Normally, many different antibodies are produced against each antigen. One reason for this diversity is that different antibodies are produced that bind to different regions (determinants) of a large antigen molecule such as HBsAg. In addition, different antibodies may be produced that bind to the same determinant. These usually differ in the tightness with which they bind to the determinant. *Affinity* is a quantitative measure of the strength of antibody-antigen binding. Usually an antibody with a higher affinity for an antigen will be more useful for immunological diagnostic tests than one with a lower affinity. Another source of heterogeneity is that there are several immunoglobulin classes or *isotypes*. Immunoglobulin G (IgG) is the most common isotype in serum. Another isotype, immunoglobulin M (IgM), is prominent early in the immune response. IgM molecules are larger than IgG molecules, and have 10 antigen-binding sites instead of the 2 that are present in IgG. Most immunoassay methods use IgG, but the claimed invention uses only IgM antibodies.

For commercial applications there are many disadvantages to using antibodies from serum. Serum contains a complex mixture of antibodies against the antigen of interest within a much larger pool of antibodies directed at other antigens. There are available only in a limited supply that ends when the donor dies. The goal of monoclonal antibody technology is to produce an unlimited supply of a single purified antibody.

The blood cells that make antibodies are *lymphocytes*. Each lymphocyte makes only one kind of antibody. During an immune response, lymphocytes exposed to their particular antigen divide and mature. Each produces a *clone* of identical daughter cells, all of which secrete the same antibody. Clones of lymphocytes, all derived from a single lymphocyte, could provide a source of a single homogeneous antibody. However, lymphocytes do not survive for long outside of the body in cell culture.

Hybridoma technology provides a way to obtain large numbers of cells that all produce the same antibody. This method takes advantage of the properties of *myeloma* cells derived from a tumor of the immune system. The cancerous myeloma cells can divide indefinitely in vitro. They also have the potential ability to secrete antibodies. By appropriate experimental manipulations, a myeloma cell can be made to fuse with a lymphocyte to produce a single hybrid cell (hence, a hybridoma) that contains the genetic material of both cells. The hybridoma secretes the same antibody that was made by its parent lymphocyte, but acquires the capability of the myeloma cell to divide and grow indefinitely in cell culture. Antibodies produced by a clone of hybridoma cells (i.e., by hybridoma

[1] *In re Wands*, Appeal No. 673-76 (Bd. Pat. App. & Int. Dec. 30, 1986).

cells that are all progeny of a single cell) are called monoclonal antibodies.[2]

B. *The Claimed Invention.*

The claimed invention involves methods for the immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. Jack R. Wands and Vincent R. Zurawski, Jr., two of the three coinventors of the present application, disclosed methods for producing monoclonal antibodies against HBsAg in United States patent No. 4,271,145 (the '145 patent), entitled "Process for Producing Antibodies to Hepatitis Virus and Cell Lines Therefor," which patent issued on June 2, 1981. The '145 patent is incorporated by reference into the application on appeal. The specification of the '145 patent teaches a procedure for immunizing mice against HBsAg, and the use of lymphocytes from these mice to produce hybridomas that secrete monoclonal antibodies specific for HBsAg. The '145 patent discloses that this procedure yields both IgG and IgM antibodies with high-affinity binding to HBsAg. For the stated purpose of complying with the best mode requirement of 35 U.S.C. §112, first paragraph, a hybridoma cell line that secretes IgM antibodies against HBsAg (the 1F8 cell line) was deposited at the American Type Culture Collection, a recognized cell depository, and became available to the public when the '145 patent issued.

The application on appeal claims methods for immunoassay of HBsAg using monoclonal antibodies such as those described in the '145 patent. Most immunoassay methods have used monoclonal antibodies of the IgG isotype. IgM antibodies were disfavored in the prior art because of their sensitivity to reducing agents and their tendency to self-aggregate and precipitate. Appellants found that their monoclonal IgM antibodies could be used for immunoassay of HbsAg with unexpectedly high sensitivity and specificity. Claims 1, 3, 7, 8, 14, and 15 are drawn to methods for the immunoassay of HBsAg using high-affinity IgM monoclonal antibodies. Claims 19 and 25–27 are for chemically modified (*e.g.*, radioactively labeled) monoclonal IgM antibodies used in the assays. The broadest method claim reads:

> 1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:
>
> contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and
>
> determining the presence of said substance in said sample;
>
> wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9 M^{-1}.

Certain claims were rejected under 35 U.S.C. §103; these rejections have not been appealed. Remaining claims 1, 3, 7, 8, 14, 15, 19, and 25–27 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the disclosure would not enable a person skilled in the art to make and use the invention without undue experimentation. The rejection is directed solely to whether the specification enables one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The position of the PTO is that data presented by Wands show that the production of high-affinity IgM anti-HBsAg antibodies is unpredictable and unreliable, so that it would require undue experimentation for one skilled in the art to make the antibodies.

III. *Analysis*

A. *Enablement by Deposit of Micro-organisms and Cell Lines.*

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. "Patents * * * are written to enable those skilled in the art to practice the invention."[3] A patent need not disclose what is well known in the art.[4] Although we review underlying facts found by the board under a "clearly erroneous" standard,[5] we review enablement as a question of law.[6]

Where an invention depends on the use of living materials such as microorganisms or

[2] For a concise description of monoclonal antibodies and their use in immunoassay see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368–71, 231 USPQ 81, 82–83 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987).

[3] *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

[4] *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

[5] *Coleman v. Dines*, 754 F.2d 353, 356, 224 USPQ 857, 859 (Fed. Cir. 1985).

[6] *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 875 (1987); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960 n.6, 220 USPQ 592, 599 n.6 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 [225 USPQ 232] (1984).

cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure. One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues.[7] Administrative guidelines and judicial decisions have clarified the conditions under which a deposit of organisms can satisfy the requirements of section 112.[8] A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public.[9] Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials.[10]

In addition to satisfying the enablement requirement, deposit of organisms also can be used to establish the filing date of the application as the prima facie date of invention,[11] and to satisfy the requirement under 35 U.S.C. §114 that the PTO be guaranteed access to the invention during pendency of the application.[12] Although a deposit may serve these purposes, we recognized, in *In re Lundak*,[13] that these purposes, nevertheless, may be met in ways other than by making a deposit.

A deposit also may satisfy the best mode requirement of section 112, first paragraph, and it is for this reason that the 1F8 hybridoma was deposited in connection with the '145 patent and the current application. Wands does not challenge the statements by the examiner to the effect that, although the deposited 1F8 line enables the public to perform immunoassays with antibodies produced by that single hybridoma, the deposit does not enable the generic claims that are on appeal. The examiner rejected the claims on the grounds that the written disclosure was not enabling and that the deposit was inadequate. Since we hold that the written disclosure fully enables the claimed invention, we need not reach the question of the adequacy of deposits.

B. *Undue Experimentation.*

Although inventions involving microorganisms or other living cells often can be enabled by a deposit,[14] a deposit is not always necessary to satisfy the enablement requirement.[15] No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.[16] Whether the specification in an application involving living cells (here, hybridomas) is enabled without a deposit must be decided on the facts of the particular case.[17]

Appellants contend that their written specification fully enables the practice of

[7] *In re Argoudelis*, 434 F.2d 1390, 1392–93, 168 USPQ 99, 101–02 (CCPA 1970).

[8] *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (Fed. Cir. 1985); *Feldman v. Aunstrup*, 517 F.2d 1351, 186 USPQ 108 (CCPA 1975), *cert. denied*, 424 U.S. 912 [188 USPQ 720] (1976); Manual of Patent Examining Procedure (MPEP) 608.01 (p)(C) (5th ed. 1983, rev. 1987). *See generally* Hampar, *Patenting of Recombinant DNA Technology: The Deposit Requirement*, 67 J. Pat. Trademark Off. Soc'y 569 (1985).

[9] *In re Jackson*, 217 USPQ 804, 807–08 (Bd. App. 1982) (strains of a newly discovered species of bacteria isolated from nature); *Feldman*, 517 F.2d 1351, 186 USPQ 108 (uncommon fungus isolated from nature); *In re Argoudelis*, 434 F.2d at 1392, 168 USPQ at 102 (novel strain of antibiotic-producing microorganism isolated from nature); *In re Kropp*, 143 USPQ 148, 152 (Bd. App. 1959) (newly discovered microorganism isolated from soil).

[10] *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (genetically engineered bacteria where the specification provided insufficient information about the amount of time and effort required); *In re Lundak*, 773 F.2d 1216, 227 USPQ 90 (unique cell line produced from another cell line by mutagenesis).

[11] *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95–96; *In re Feldman*, 517 F.2d at 1355, 186 USPQ at 113; *In re Argoudelis*, 434 F.2d at 1394–96, 168 USPQ at 103–04 (Baldwin, J. concurring).

[12] *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95–96; *In re Feldman*, 517 F.2d at 1354, 186 USPQ at 112.

[13] *In re Lundak*, 773 F.2d at 1222, 227 USPQ at 95–96.

[14] *In re Argoudelis*, 434 F.2d at 1393, 168 USPQ at 102.

[15] *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977).

[16] *Id.* at 1186–87, 194 USPQ at 525; *Merck & Co. v. Chase Chem. Co.*, 273 F.Supp. 68, 77, 155 USPQ 139, 146 (D.N.J. 1967); *Guaranty Trust Co. v. Union Solvents Corp.*, 54 F.2d 400, 403–06, 12 USPQ 47, 50–53 (D. Del. 1931), *aff'd*, 61 F.2d 1041, 15 USPQ 237 (3d Cir. 1932), *cert. denied*, 288 U.S. 614 (1933); MPEP 608.01(p)(C) ("No problem exists when the microorganisms used are known and readily available to the public.").

[17] *In re Jackson*, 217 USPQ at 807; *see In re Metcalfe*, 410 F.2d 1378, 1382, 161 USPQ 789, 792 (CCPA 1969).

their claimed invention because the monoclonal antibodies needed to perform the immunoassays can be made from readily available starting materials using methods that are well known in the monoclonal antibody art. Wands states that application of these methods to make high-affinity IgM anti-HBsAg antibodies requires only routine screening, and that does not amount to undue experimentation. There is no challenge to their contention that the starting materials (i.e., mice, HBsAg antigen, and myeloma cells) are available to the public. The PTO concedes that the methods used to prepare hybridomas and to screen them for high-affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed in the '145 patent and in the current application. This is consistent with this court's recognition with respect to another patent application that methods for obtaining and screening monoclonal antibodies were well known in 1980.[18] The sole issue is whether, in this particular case, it would require undue experimentation to produce high-affinity IgM monoclonal antibodies.

Enablement is not precluded by the necessity for some experimentation such as routine screening.[19] However, experimentation needed to practice the invention must not be undue experimentation.[20] "the key word is 'undue,' not 'experimentation.' "[21]

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 [172 USPQ 257] (1972)]. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * *.[22]

The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.[23] Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. The board concluded that undue experimentation would be needed to practice the invention on the basis of experimental data presented by Wands. These data are not in dispute. However, Wands and the board disagree strongly on the conclusion that should be drawn from that data.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*.[24] They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.[25]

In order to understand whether the rejection was proper, it is necessary to discuss further the methods for making specific monoclonal antibodies. The first step for making monoclonal antibodies is to immunize an animal. The '145 patent provides a detailed description of procedures for immunizing a specific strain of mice against HBsAg. Next the spleen, an organ rich in lymphocytes, is removed and the lymphocytes are separated from the other spleen cells. The lymphocytes are mixed with myeloma cells, and the mixture is treated to cause a few of the cells to fuse with each other. Hybridoma cells that secrete the desired antibodies then must be isolated from the enormous number of other cells in the mixture. This is done through a series of screening procedures.

The first step is to separate the hybridoma cells from unfused lymphocytes and myeloma cells. The cells are cultured in a medi-

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[18] *Hybritech*, 802 F.2d at 1384, 231 USPQ at 94.

[19] *Id.*; *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); *In re Angstadt*, 537 F.2d at 502-504, 190 USPQ at 218; *In re Geerdes*, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); *Mineral Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916).

[20] *Hybritech*, 802 F.2d at 1384, 231 USPQ at 94; *W.L. Gore*, 721 F.2d at 1557, 220 USPQ at 316; *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977) (Miller, J., concurring).

[21] *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219.

[22] *In re Jackson*, 217 USPQ at 807.

[23] *See Hybritech*, 802 F.2d at 1384, 231 USPQ at 94; *Atlas Powder*, 750 F.2d at 1576, 224 USPQ at 413.

[24] *Ex parte Forman*, 230 USPQ at 547.

[25] *Id.*; *see In re Colianni*, 561 F.2d at 224, 195 USPQ at 153 (Miller, J., concurring); *In re Rainer*, 347 F.2d 574, 577, 146 USPQ 218, 221 (CCPA 1965).

um in which all the lymphocytes and myeloma cells die, and only the hybridoma cells survive. The next step is to isolate and clone hybridomas that make antibodies that bind to the antigen of interest. Single hybridoma cells are placed in separate chambers and are allowed to grow and divide. After there are enough cells in the clone to produce sufficient quantities of antibody to analyze, the antibody is assayed to determine whether it binds to the antigen. Generally, antibodies from many clones do not bind the antigen, and these clones are discarded. However, by screening enough clones (often hundreds at a time), hybridomas may be found that secrete antibodies against the antigen of interest.

Wands used a commercially available radioimmunoassay kit to screen clones for cells that produce antibodies directed against HBsAg. In this assay the amount of radioactivity bound gives some indication of the strength of the antibody-antigen binding, but does not yield a numerical affinity constant, which must be measured using the more laborious Scatchard analysis. In order to determine which anti-HBsAg antibodies satisfy all of the limitations of appellants' claims, the antibodies require further screening to select those which have an IgM isotype and have a binding affinity constant of at least 10^9 M^{-1}.[26] The PTO does not question that the screening techniques used by Wands were well known in the monoclonal antibody art.

During prosecution Wands submitted a declaration under 37 C.F.R §1.132 providing information about all of the hybridomas that appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas that made antibodies specific for HBsAg. Antibodies that bound at least 10,000 cpm in the commercial radioimmunoassay were classified as "high binders." Using this criterion, 143 high-binding hybridomas were obtained. In the declaration, Wands stated that [27]

It is generally accepted in the art that, among those antibodies which are binders with 50,000 cpm or higher, there is a very high likelihood that high affinity (Ka [greater than] 10^9 M^{-1}) antibodies will be found. However, high affinity antibodies can also be found among high binders of between 10,000 and 50,000, as is clearly demonstrated in the Table.

The PTO has not challenged this statement.

The declaration stated that a few of the high-binding monoclonal antibodies from two fusions were chosen for further screening. The remainder of the antibodies and the hybridomas that produced them were saved by freezing. Only nine antibodies were subjected to further analysis. Four (three from one fusion and one from another fusion) fell within the claims, that is, were IgM antibodies and had a binding affinity constant of at least 10^9 M^{-1}. Of the remaining five antibodies, three were found to be IgG, while the other two were IgM for which the affinity constants were not measured (although both showed binding well above 50,000 cpm).

Apparently none of the frozen cell lines received any further analysis. The declaration explains that after useful high-affinity IgM monoclonal antibodies to HBsAg had been found, it was considered unnecessary to return to the stored antibodies to screen for more IgMs. Wands says that the existence of the stored hybridomas was disclosed to the PTO to comply with the requirement under 37 C.F.R. §1.56 that applicants fully disclose all of their relevant data, and not just favorable results.[28] How these stored hybridomas are viewed is central to the positions of the parties.

The position of the board emphasizes the fact that since the stored cell lines were not completely tested, there is no proof that any of them are IgM antibodies with a binding affinity constant of at least 10^9 M^{-1}. Thus, only 4 out of 143 hybridomas, or 2.8 percent, were *proved* to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the board as evidence that appellants' methods were not predictable or reproducible. The board concludes that Wands' low rate of demonstrated success shows that a person skilled in the art would have to

[26] The examiner, the board, and Wands all point out that, technically, the strength of antibody-HBsAg binding is measured as *avidity*, which takes into account multiple determinants on the HBsAg molecule, rather than affinity. Nevertheless, despite this correction, all parties then continued to use the term "affinity." We will use the terminology of the parties. Following the usage of the parties, we will also use the term "high-affinity" as essentially synonymous with "having a binding affinity constant of at least 10^9 M^{-1}."

[27] A table in the declaration presented the binding data for antibodies from every cell line. Values ranged from 13,867 to 125,204 cpm, and a substantial proportion of the antibodies showed binding greater than 50,000 cpm. In confirmation of Dr. Wand's statement, two antibodies with binding less than 25,000 cpm were found to have affinity constants greater than 10^9 M^{-1}.

[28] *See Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 220 USQ 98 (Fed. Cir. 1983).

engage in undue experimentation in order to make antibodies that fall within the claims.

Wands views the data quite differently. Only nine hybridomas were actually analyzed beyond the initial screening for HBsAg binding. Of these, four produced antibodies that fell within the claims, a respectable 44 percent rate of success. (Furthermore, since the two additional IgM antibodies for which the affinity constants were never measured showed binding in excess of 50,000 cpm, it is likely that these also fall within the claims.) Wands argues that the remaining 134 unanalyzed, stored cell lines should not be written off as failures. Instead, if anything, they represent partial success. Each of the stored hybridomas had been shown to produce a high-binding antibody specific for HBsAg. Many of these antibodies showed binding above 50,000 cpm and are thus highly likely to have a binding affinity constant of at least 10^9 M^{-1}. Extrapolating from the nine hybridomas that were screened for isotype (and from what is well known in the monoclonal antibody art about isotype frequency), it is reasonable to assume that the stored cells include some that produce IgM. Thus, if the 134 incompletely analyzed cell lines are considered at all, they provide some support (albeit without rigorous proof) to the view that hybridomas falling within the claims are not so rare that undue experimentation would be needed to make them.

The first four fusion attempts were failures, while high-binding antibodies were produced in the next six fusions. Appellants contend that the initial failures occurred because they had not yet learned to fuse cells successfully. Once they became skilled in the art, they invariably obtained numerous hybridomas that made high-binding antibodies against HBsAg and, in each fusion where they determined isotype and binding affinity they obtained hybridomas that fell within the claims.

Wands also submitted a second declaration under 37 C.F.R. §1.132 stating that after the patent application was submitted they performed an eleventh fusion experiment and obtained another hybridoma that made a high-affinity IgM anti-HBsAg antibody. No information was provided about the number of clones screened in that experiment. The board determined that, because there was no indication as to the number of hybridomas screened, this declaration had very little value. While we agree that it would have been preferable if Wands had included this information, the declaration does show that when appellants repeated their procedures they again obtained a hybridoma that produced an antibody that fit all of the limitations of their claims.

[1] We conclude that the board's interpretation of the data is erroneous. It is strained and unduly harsh to classify the stored cell lines (each of which was proved to make high-binding antibodies against HBsAg) as failures demonstrating that Wands' methods are unpredictable or unreliable.[29] At worst, they prove nothing at all about the probability of success, and merely show that appellants were prudent in not discarding cells that might someday prove useful. At best, they show that high-binding antibodies, the starting materials for IgM screening and Scatchard analysis, can be produced in large numbers. The PTO's position leads to the absurd conclusion that the more hybridomas an applicant makes and saves without testing the less predictable the applicant's results become. Furthermore, Wands' explanation that the first four attempts at cell fusion failed only because they had not yet learned to perform fusions properly is reasonable in view of the fact that the next six fusions were all successful. The record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens.

[2] When Wands' data is interpreted in a reasonable manner, analysis considering the factors enumerated in *Ex parte Forman* leads to the conclusion that undue experimentation would not be required to practice the invention. Wands' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known.

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that un-

[29] Even if we were to accept the PTO's 2.8% success rate, we would not be required to reach a conclusion of undue experimentation. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff.

due experimentation would be defined in terms of the number of hybridomas that were never screened. Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics. Wands carried out this entire procedure three times, and was successful each time in making at least one antibody that satisfied all of the claim limitations. Reasonably interpreted, Wands' record indicates that, in the production of high-affinity IgM antibodies against HBsAG, the amount of effort needed to obtain such antibodies is not excessive. Wands' evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.[30]

IV. *Conclusion*

Considering all of the factors, we conclude that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. Accordingly, the rejection of Wands' claims for lack of enablement under 35 U.S.C. §112, first paragraph, is reversed.

REVERSED

Newman, J., concurring in part, dissenting in part.

A

I concur in the court's holding that additional samples of hybridoma cell lines that produce these high-affinity IgM monoclonal antibodies need not be deposited. This invention, as described by Wands, is not a selection of a few rare cells from many possible cells. To the contrary, Wands states that all monoclonally produced IgM antibodies to hepatitis B surface antigen have the desired high avidity and other favorable properties, and that all are readily preparable by now-standard techniques.

Wands states that his United States Patent No. 4,271,145 describes fully operable techniques, and is distinguished from his first four failed experiments that are referred to in the Rule 132 affidavit. Wands argues that these biotechnological mechanisms are relatively well understood and that the preparations can be routinely duplicated by those of skill in this art, as in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987). I agree that it is not necessary that there be a deposit of multiple exemplars of a cell system that is readily reproduced by known, specifically identified techniques.

B

I would affirm the board's holding that Wands has not complied with 35 U.S.C. §112, first paragraph, in that he has not provided data sufficient to support the breadth of his generic claims. Wands' claims on appeal include the following:

> 19. Monoclonal high affinity IgM antibodies immunoreactive with HBsAg determinants, wherein said antibodies are coupled to an insoluble solid phase, and wherein the binding affinity constant of said antibodies for said HBsAg determinants is at least 10^9 M^{-1}.
>
> 26. Monoclonal high affinity IgM antibodies immunoreactive with hepatitis B surface antigen.

Wands states that he obtained 143 "high binding monoclonal antibodies of the right specificity" in the successful fusions; although he does not state how they were determined to be high binding or of the right specificity, for Wands also states that only nine of these 143 were tested.

Of these nine, four (three from one fusion and one from another fusion) were found to have the claimed high affinity and to be of the IgM isotype. Wands states that the other five were either of a different isotype or their affinities were not determined. (This latter statement also appears to contradict his statement that all 143 were "high binding".)

Wands argues that a "success rate of four out of nine", or 44.4%, is sufficient to support claims to the entire class. The Commissioner deems the success rate to be four out of 143, or 2.8%; to which Wands responds with statistical analysis as to how unlikely it is that Wands selected the only four out of 143 that worked. Wands did not, however, prove the right point. The question is whether Wands, by testing nine out of 143 (the Commissioner points out that the randomness of the sample was not established), and finding that four out of the nine had the desired properties, has provided sufficient experimental support for the breadth of the requested claims, in the context that "experi-

[30] *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982).

ments in genetic engineering produce, at best, unpredictable results", quoting from *Ex parte Forman*, 230 USPQ 546, 547 (Bd.Pat.App. and Int. 1986).

The premise of the patent system is that an inventor, having taught the world something it didn't know, is encouraged to make the product available for public and commercial benefit, by governmental grant of the right to exclude others from practice of that which the inventor has disclosed. The boundary defining the excludable subject matter must be carefully set: it must protect the inventor, so that commercial development is encouraged; but the claims must be commensurate with the inventor's contribution. Thus the specification and claims must meet the requirements of 35 U.S.C. §112. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 23-24 (CCPA 1970).

As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112.

Wands is not claiming a particular, specified IgM antibody. He is claiming all such monoclonal antibodies in assay for hepatitis B surface antigen, based on his teaching that such antibodies have uniformly reproducible high avidity, free of the known disadvantages of IgM antibodies such as tendency to precipitate or aggregate. It is incumbent upon Wands to provide reasonable support for the proposed breadth of his claims. I agree with the Commissioner that four exemplars shown to have the desired properties, out of the 143, do not provide adequate support.

Wands argues that the law should not be "harsher" where routine experiments take a long time. However, what Wands is requesting is that the law be less harsh. As illustrated in extensive precedent on the question of how much experimentation is "undue", each case must be determined on its own facts. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976); *In re Cook*, 439 F.2d 730, 734-35, 169 USPQ 298, 302-03 (CCPA 1971).

The various criteria to be considered in determining whether undue experimentation is required are discussed in, for example, *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1971); *In re Rainer*, 347 F.2d 574, 146 USPQ 218 (CCPA 1965); *Ex parte Forman*, 230 USPQ at 547. Wands must provide sufficient data or authority to show that his results are reasonably predictable within the scope of the claimed generic invention, based on experiment and/or scientific theory. In my view he has not met this burden.

Patent and Trademark Office
Trademark Trial and Appeal Board

In re Johanna Farms Inc.

Serial No. 542,343

Decided June 30, 1988

JUDICIAL PRACTICE AND PROCEDURE

1. Procedure — Prior adjudication — In general (§410.1501)

Trademark Trial and Appeal Board's prior decision upholding examiner's refusal to register proposed mark "La Yogurt" does not preclude registration of mark pursuant to subsequent application, since applicant, by presenting survey evidence and consumer letters regarding issue of how purchasers perceive proposed mark, has demonstrated that instant factual situation is different from situation presented in prior proceeding.

TRADEMARKS AND UNFAIR TRADE PRACTICES

2. Types of marks — Non-descriptive — Particular marks (§327.0505)

Term "La Yogurt," with "yogurt" disclaimed, is registrable, since word "yogurt" is common English generic term rather than corruption or misspelling of French word for yogurt, since examining attorney failed to meet burden of showing clear evidence of generic use of mark as whole, and since evidence of record, including survey and consumer letters to applicant, demonstrates that primary significance of "La Yogurt" to majority of relevant public is that of brand name rather than generic term.